REMARKS

Applicants respectfully request entry of the Amendment and reconsideration of the rejection of the claims. Claims 2 and 5-41 have been cancelled without prejudice or disclaimer. Claims 5, 9, 30 and 31 were previously withdrawn due to restriction requirement. Applicants reserve the right to pursue the subject matter of all of the cancelled claims in one or more continuation applications.

Claims 1 and 54 have been amended. Support for the Amendment is found throughout the specification as originally filed, including at page 53, lines 6-7. Applicants submit no new matter has been introduced by the foregoing Amendment.

Utility

Claims 1, 3, 4, and 42-54 were rejected under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, as lacking utility. The Office Action alleges the claimed polypeptide does not have a specific and substantial utility. Applicants respectfully traverse this rejection.

The Examiner alleges the claimed polypeptide lacks specific and substantial utility because the actual function of the polypeptide has not been disclosed. Applicants do not agree.

Applicants respectfully remind the Examiner that Applicants do not have to provide evidence to establish that the asserted utility is true beyond a reasonable doubt. In re Irons, 340 F2d 974, 978 (CCPA 1965). Nor do Applicants have to provide evidence that establishes the asserted utility as a matter of statistical certainty. Nelson v. Bowler, 626 F2d 863, 856-867 (CCPA 1980). Rather, Applicants have the burden of presenting evidence that leads a person of ordinary skill in the art to conclude the asserted utility is more likely than not to be true. MPEP § 2107.02 (emphasis in original). By requiring Applicants to teach the actual function of the claimed polypeptide, the Examiner is in effect requiring empirical evidence of biological activity. Applicants submit that empirical evidence of biological activity is not required to establish utility. Applicants direct the Examiner's attention to Example 10 of the Revised Interim Utility Guidelines training materials. In Example 10, the asserted utility of a putative DNA ligase was established based on having a % homology to known DNA ligases. Thus, Applicant's submit that the standard to establish utility does not require empirical evidence of utility.

Applicants' submit in view of hBAZF's expression pattern and structural similarity to mouse BAZF, one skilled in the art would expect hBAZF to function as a transcriptional repressor during angiogenesis. Brenner et al. teach that pairwise sequence comparison methods are capable of detecting almost all relationships between proteins whose sequence identities are greater than 30% (Brenner et al., abstract at page 6073 and figure 3 at page 6075; copy enclosed). The Brenner et al. study validated the use of sequence comparison methods to establish that % sequence identity comparisons greater than 30% are predictive of shared function. Mouse BAZF was known to be a homolog of Bcl-6 and function as a transcriptional repressor (Okabe et al., abstract at page 4235). Human BAZF has 83% amino acid sequence identity with mouse BAZF and like its mouse homolog contains a BTB/POZ domain and five Kruppel-like zinc finger motif repeats. Applicants therefore submit one skilled in the art would conclude that hBAZF polypeptide more likely than not has transcriptional repressor activity.

Applicants submit hBAZF has both specific and substantial utility as a marker for angiogenic activity. Tumor cells exploit angiogenesis to facilitate tumor growth (page 2, lines 15). The suspension of endothelial cells in type I collagen gels is commonly used by those skilled in the art as a model of angiogenesis. Applicants utilized this model of angiogenesis to identify molecules, including hBAZF, which were upregulated during endothelial differentiation into tubelike structures (*see*, page 4, lines 6-9 of the specification). Applicants teach that hBAZF mRNA is upregulated 2.1 fold in HUVE cells grown embedded in collagen gels. (page 126, lines 14-31). In contrast, hBAZF mRNA is not upregulated in HUVE cells grown as a monolayer on collagen (page 53, lines 12-16). Since hBAZF mRNA is highly expressed during vessel morphogenesis (page 53, lines 16-18), Applicants submit one skilled in the art would conclude that hBAZF polypeptide is more likely than not a marker for angiogenesis.

An angiogenesis marker such as hBAZF has utility in diagnostic assays. For example, Applicants disclose that detecting an increase in AAP(Angiogenesis Associated Protein) in a biological sample is useful for determining if an individual is afflicted with a disease or disorder, such as cancer (page 113, lines 25-32). Applicants also disclose that angiogenesis associated proteins (AAP) and nucleic acids, such as for example hBAZF, are useful in treating tumors and cancers (page 51, lines 11-14). Applicants submit these utilities are both specific and substantial to the claimed invention.

The Examiner alleges that since the instant invention is based on the differential expression of mRNA, the use of the protein in terms of a marker for angiogenesis cannot be determined because there are no experiments showing differential expression at the protein level. Applicants do not agree.

Applicants submit it is well known in the art that the primary role of RNA transcripts is to serve as templates for protein synthesis (*see*, page 7, lines 1-4 of Alberts, B. 2002. *Molecular Biology of the Cell.* Garland Science, New York). In the HUVE collagen gel angiogenesis model described above, Zlot et al. showed that an increase in stanniocalcin 1 mRNA correlates with an increase in stanniocalcin 1 protein (Zlot et al., 2003, *J. Biol. Chem.*, 278:47654-47659 at page 47655 and Fig. 1A and 1B; copy enclosed). In human transitional cell carcinomas, for example, Orntoft et al. showed a significant correlation between DNA copy number, mRNA expression, and protein level and showed with few exceptions significant correlation ($p<0.005$) between transcript alterations and protein levels (Orntoft et al., 2002, *Mol. Cell. Proteomics* 1:37-45; copy enclosed). In tumor tissues, Horikoshi et al. showed the amount of thymidylate synthase gene expression was directly proportional to the content of thymidylate synthase protein (Horikoshi et al., 1992, *Cancer* Res., 52:108-116; copy enclosed). In yeast, Futcher et al. showed a statistically significant correlation between protein abundance and mRNA abundance and concluded the abundance of mRNA is a predictor of protein abundance (Futcher et al., 1999, *Mol. Cell. Biol.* 19:7357-7368; copy enclosed). See, for example, Fig. 2 in Futcher et al. Applicants therefore submit one skilled in the art would expect that an increase in hBAZF mRNA expression would more likely than not correlate with an increase in hBAZF polypeptide expression.

Applicants have shown the specification provides specific and substantial utility for a polypeptide comprising SEQ ID NO:4. Applicants demonstrated hBAZF is a marker for angiogenesis and provided evidence that an increase in hBAZF mRNA expression correlates with an increase in hBAZF polypeptide expression. Antibodies to the claimed polypeptide are useful in the diagnosis of disease or disorders associated with angiogenesis, such as cancer. These utilities are specific to the subject matter claimed and define a real world use.

For at least these reasons, Applicants submit one skilled in the art would know how to use the claimed invention because the claimed invention is supported by specific and substantial

utility. Withdrawal of the utility rejection under 35 U.S.C. § 101 and 35 U.S.C. §112, first paragraph, is respectfully requested.

Written Description

Claims 1, 3-4, and 42-54 were rejected under 35 U.S.C. § 112, first paragraph, as lacking written description. The Office Action alleges that the written description for sequences that are at least 84% identical to that of SEQ ID NO: 4 requires more than the base sequence of SEQ ID NO: 4. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Claim 1 has been recited to set forth the functional and structural characteristics of polypeptides at least 84% identical to that of SEQ ID NO: 4. As amended, claim 1 sets forth that the claimed polypeptides comprise five Kruppel-like zinc finger motif repeats and a BTB/POZ domain. Applicants provide a description of SEQ ID NO: 4 and its characteristics at page 53, lines 6-7, "Human BAZF contains five Kruppel-like zinc finger motif repeats and a BTB/POZ domain." In addition, Applicants teach that hBAZF is upregulated in an angiogenic model commonly used in the art (see, page 53, lines 12-13 of the specification).

Applicants define and teach variants of the polypeptides of the present invention at page 74, lines 1-32, and page 75, lines 1- 20 of the specification. More particularly, Applicants teach the following:

> An AAP polypeptide variant will have at least about 80% amino acid sequence identity, preferably at least about 81% amino acid sequence identity, more preferably at least about 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% amino acid sequence identity and most preferably at least about 99% amino acid sequence identity with a full-length native sequence AAP polypeptide sequence.

Page 74, lines 15-20 of the specification.

Based on the above, Applicants maintain the specification provides sufficient written description of the claimed sequences. Withdrawal of this rejection is respectfully requested.

CONCLUSION

Applicants submit that the claims are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative if prosecution may be assisted thereby.

Respectfully submitted,

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Date: September 20, 2004

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